Comments from the Allergenic Products Manufacturers Association (APMA)
Presented to the Allergenic Product Advisory Committee
March 5, 2001
Presented by Shirley Williamson, President, APMA

PRECIPITATION IN ALLERGENIC EXTRACTS

DEFINITIONS:

Precipitation in allergenic extracts refers to the phenomenon whereby intrinsic and initially soluble components of the solution become insoluble and form visibly evident sediment over time

Particulate in allergenic extracts refers to extrinsic particles present that are not intrinsic to the extract itself

HISTORY:

Precipitation has been recognized by industry as a product characteristic for over 30 years

Over the years, manufacturers have attempted to characterize/solve the problem with very limited progress/success

Precipitation was raised to a compliance level beginning with observations made on 483 forms beginning in late fall, 1999

Representatives from several of the manufacturers met with CBER personnel in October, 2000 to discuss the issues involved

TYPES OF PRODUCTS INVOLVED

All types of allergenic extracts reportedly form precipitate

However, precipitation occurs most commonly in

- aqueous (non-glycerinated) extracts
- more highly concentrated extracts (1:10 w/v, 1:20 w/v, 40,000 PNU/mL) but will also occur in diluted form

- many pollen extracts, but some genera seem more prone than others

VISUAL APPEARANCE OF PRECIPITATE

Precipitate appearance varies, depending upon the product

Appearance has been described as:

Filamentous (Stringy, fiber-like)
Granular (Sand-like, generally settled on the bottom)
Crystalline (Angular, generally clear, often suspended)
Cloudy (Diffuse, rather than distinct particles, hazy appearance)
Flaky (Flat pieces, often has some color)
Film (Layer on the top or bottom of solution)

Presence of precipitate may appear in one lot of product from a given lot of source material but not in the next lot extracted from the same lot of source material, at the same concentration using the same manufacturing processes

CHARACTERIZATION/ANALYSES OF PRECIPITATE

Most manufacturers have reported using some method to examine precipitated extracts for the presence of microorganisms (such as microscopic exam after staining or a sterility test) and there has never been an occurrence when the precipitation was found to be microbial contamination

Major difficulties in characterizing precipitate result from:

- collecting sufficient quantities to analyze (although the precipitate appears "heavy", there is small amount in the volume)

- adequate cleaning of the precipitate to thoroughly separate the precipitate from the soluble extract often results in additional loss of the precipitated material or dissolution of the precipitate into the cleaning solvent

Limited characterization results have been obtained

- some data suggests that the precipitates consist of chemicals derived from the source materials such as polyphenols, or flavinoids that will agglomerate proteins, or agglomerated protein/carbohydrate to form sediments

- some crystalline precipitate has been identified as calcium oxalate

EFFECT OF PRECIPITATE ON SUITABILITY FOR USE

Safety:

- No "controlled" studies have been performed, but none of the manufacturers have reported any adverse events or patient safety issues associated with the presence of precipitate in extract

Potency:

- Data presented in October meeting with CBER on Standardized Timothy, Short Ragweed, and Dog extracts did not indicate loss of potency when extract precipitated

Composition

- Data presented in October meeting with CBER and obtained subsequently on various extracts did not indicate changes in the protein profiles of various extracts that had precipitated

- Profiles were determined by SDS-PAGE or IEF

Protein Content

- Data presented in October meeting with CBER and obtained subsequently on various extracts did not indicate changes on the protein content of various extracts that had precipitated

AGREEMENTS RESULTING FROM OCTOBER MEETING

1. Manufacturers agreed that extracts with any visible precipitate would not be shipped to customers

2. Manufacturers agreed to include common verbiage in product instructions regarding precipitate

3. Manufacturers and CBER personnel agreed to continue studies to characterize precipitates

4. Manufacturers and CBER personnel agreed to standardize the Error and Accident reporting (now Biological Product Deviation Report)

CURRENT INITIATIVES BY INDUSTRY

1. Inspect product just prior to shipping to customers and do not ship the product if precipitate is visible; effects of this initiative include:

    - product shortages when manufacturer must discard product – these shortages will result in disruption of product supply and will affect the treatment regimes of patients undergoing immunotherapy with that product

    - reduction in product lines as manufacturers will discontinue products that tend to precipitate

    - increased costs to the customers to offset the increased losses

    - move towards use of glycerinated extracts and/or more dilute non-glycerinated products

2. Add verbiage to product labeling regarding the presence of precipitate

    - propose adding the wording in the **Dosage and Administration** section of the instructions (using verbiage as given in 21 CFR § 201.57)

    - this will require submission and approval of each insert used by each manufacturer

3. Continue evaluation of products with existing technology

    - this includes protein content, protein profiles (SDS-PAGE or IEF), potency assays
    - may expand to include immuno-blots to evaluate effect on allergens

4. Work with CBER personnel to expand use to new technologies to evaluate these products

5. Develop alternate manufacturing methods to prevent formation of precipitate

    - very long term as extensive studies would be required for approval of modifications to existing licenses